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c) detecting an output signal;

d) processing said detected output signal to determine the presence of said target analytes.

REMARKS

Claims 11-27 are pending in the application.

As a preliminary matter, Applicants thank the Examiner for holding in abeyance the objections to the defects in the drawings as stated on form PTO-948 until otherwise allowable subject matter is found.

Independent claims 11, 12, 13 and 27 have been amended for technical clarity and find support throughout the specification, particularly at page 90, lines 22-33 and page 114, lines 31-32. Claims 14 and 15 have been corrected to provide sufficient antecedent basis. Claim 25 has been amended, in reply to the Examiner's objection, to place the claim in proper form. No new matter is added by the amendments. Accordingly, Applicants respectfully request entry of all amendments into the instant application.

Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the pending claims is respectfully requested for the reasons that follow.

Compliance with 37 C.F.R. §§ 1.821-1.825

Applicants have attached hereto substitute sheets of the amended Sequence Listing in response to the Office Action and Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. Please amend the specification on page 128, immediately preceding the claims, by deleting the previously submitted "Sequence Listing" in its entirety and inserting the enclosed text entitled "SEQUENCE LISTING."

The amendment is accompanied by a substitute floppy disc containing SEQUENCE ID NUMBERS 1-7 in computer readable form, which includes all previously submitted data. The computer readable sequence listing was prepared through use of the software program "PatentIn" provided by the PTO. The information contained in the substitute computer readable disc is identical to that of the substitute paper copy. This amendment adds no new matter.

Accordingly, Applicants submit that this amendment, the accompanying computer readable sequence listing, and the paper copy serves to place the application in compliance with the rules 37 C.F.R. § 1.821-1.825.

Claim Objections

Claim 25 is objected to because of the use of the abbreviation "DC". Claim 25 has been amended to incorporate language that defines the terms "AC" and "DC". Accordingly, Applicants request withdrawal of the objection.

Rejections Under 35 U.S.C. § 112, second paragraph.

Claims 14-15 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Specifically, the Examiner holds that claims 14 and 15 have insufficient antecedent basis in the claims.

Applicants have corrected claims 14 and 15 to depend from claims 11 or 12. The claims as amended have sufficient antecedent basis to comply with the requirements of § 112. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 14 and 15 under 35 U.S.C. § 112, second paragraph.

Claim 16 is rejected under 35 U.S.C. § 112, second paragraph because the Examiner considers the term "higher harmonic analysis" as being indefinite. The Examiner agrees with Applicants' argument that "higher harmonic analysis" is a term of art but contends that the

specification and the claims fail to adequately define the term to reasonably apprise a person of ordinary skill in the art as to the scope of the claim. Applicants respectfully traverse.

√The term "higher harmonics" is a phrase well known in the field of electrochemistry and physics. Those skilled in the art and the specification define "higher harmonics" as frequencies that are the multiples of the fundamental frequency (see Specification, page 94, third paragraph, lines 6-9). In electrochemistry, the fundamental frequency is the frequency of the applied input signal (see Specification, page 94, lines 21-24). The specification recites that detection at higher harmonic frequencies may range from second to tenth or greater, but with particular preference for the third, fourth and fifth harmonics (see Specification, page 94, lines 21-31). Thus, with guidance from the specification, a person skilled in the art can evaluate which multiple of the fundamental frequency is best suited for characterizing the response of an electrode to an electronic input signal.

Applicants submit that in view of the knowledge of those skilled in the art and the disclosures within the specification, the language of the claim reasonably apprises those skilled in the art the scope of claim 16. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 16 under 35 U.S.C. § 112, second paragraph.

<u>Rejections Under 35 U.S.C. § 102(e)</u>

Claims 11 and 13 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Megerle et al., U.S. Pat. No. 5,874,046 (hereinafter "Megerle"). Applicants respectfully traverse.

√ As a preliminary matter, Applicants direct the Examiner to an error in citation of Meade, which is referenced in Megerle. In the Office Action, Examiner refers to Meade, U.S. Pat. No. 6,013,459 issued on January 11, 2000 as a reference cited by Megerle. However, Megerle refer to Meade et al. WO 95/15971 and a publication entitled "Electron Transfer through DNA with Rutheneum Donors and Acceptors" (Angewandte Chemie-International

Edition in English, 34(3), pp352-354, 1995) (column 4, lines 50-61). The Megerle patent issued on February 23, 1999, which antedates the issue date of Meade et al. U.S. Pat. No. 6,013,459. Accordingly, in the absence of clarity as to the cited references, Applicants restrict the following discussion to subject matter disclosed within Megerle.

Megerle disclose a method for identifying target organisms using a biosensor. The sensor comprises at least one electrode having a single stranded oligonucleotide complementary to a target organism's DNA or RNA. The single stranded oligonucleotide has at least one electron donor moiety and one electron acceptor moiety (ETM). Hybridization of the target nucleic acid to the ETM bearing single stranded oligonucleotide alters the electron transfer properties of the hybridized complex, which alters the electrical properties of the electrode. Megerle suggest use of various techniques, such as cyclic voltammetry, pulse polarography, and/or impedance measurements, to detect electron transfer between the electron transfer moieties and the electrode (column 6, line 51-65). These techniques cited by Megerle detect electronic output signal of the electrode and do not require processing of the electronic output signal, for example to separate out background noise.

Claims 11 and 13 as amended recites a method of determining the presence of target analytes, such as a nucleic acid. The claims provide for an array of electrodes with a least one of the electrodes comprising an assay complex comprised of a capture binding ligand covalently attached to the electrode, a target analyte, and an electron transfer moiety. Formation of a complex comprising the capture binding ligand, the target analyte and the electron transfer moiety alters the electrical properties of the electrode, which are measured by applying an electronic input signal and detecting the electronic output signal. In contrast to Megerle, claims 11 and 13 recite the step of processing the electronic output signal. These signal processing methods include techniques such as higher harmonic analysis using Fast Fourier Transforms (FFT) and peak recognition schemes, which provide the advantage of

separating out background noise from the output signal or maximizing the electronic signal arising from electron transfer through the electron transfer moieties.

Anticipation of a claim requires that the cited references teach each and every element of the claim. See M.P.E.P. § 2134. Thus, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. See Verdegaal Bros. V. Union Oil of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Megerle teach detecting an electronic output signal from a biosensor, but do not teach processing of detected electronic output signals. In contrast, claim 11 or 13 teaches processing of the detected output signal of the electrode to enhance detection of target analytes in a sample. Thus, Megerle fail to teach each and every element of claims 11 and 13, and thus do not anticipate claim 11 or 13. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

Rejections Under 35 U.S.C. § 103(a)

Claims 12, 19, 21, and 23-27 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by Megerle in view of Meade, U.S. Pat. No. 6,013,459. The Examiner further contends that processing of an electronic output signal by peak recognition and signal averaging are inherent properties of alternating currents (AC) and direct currents (DC) (Physics: Principles With Applications, 3rd ed., Douglas C. Giancoli, 1991, Prentice Hall, Englewood Cliffs, New Jersey)(hereinafter "Giancoli"). Applicants respectfully traverse.

Teachings of Megerle have been summarized above.

Meade teach an electrode having a binding ligand that binds target analytes. Presence of an electron transfer moiety in the complex formed between the binding ligand and target analyte alters the electronic properties of the electrode. Meade suggests detecting the electrode characteristics by a variety of techniques, including cyclic voltammetry and AC

voltammetry (column 20). As argued above, these techniques do not require processing of a detected electronic output signal. Meade do suggest, however, use of lock-in amplifiers to obtain improvements of the signal over noise, especially when employing frequency dependent methods (column 21, third paragraph).

In brief, lock-in amplifiers detect signals obscured by high background noise by measuring the signal at a narrow bandwidth that encompasses the frequency of the output signal being measured. Improvements to the signal over the noise derive from avoidance of significant background noise generally present at low frequencies and is accomplished by measuring the signal at a narrow bandwidth of higher frequencies. In Meade, further improvements of the signal over noise are possible because of the fast electron transfer rates of electron transfer moieties, which allows detection of electronic signals at even higher frequencies than for complexes not containing electron transfer moieties. Thus, a lock-in amplifier detects a signal output having low noise but without subsequently processing the detected electronic output signal.

Giancoli defines the properties of AC and DC currents. For an AC current source, the "peak current" is the maximum current generated by the source while the "peak voltage" is the maximum potential, $V_{o,}$ between which the current oscillates. The average current over time sums to zero since the current flow reverses during a single cycle. What Giancoli explains is the basic characteristics of an AC current, and thus does not describe how to measure and characterize the response of an electrode to an applied current.

In the instant application, claims 12 and 27 as amended recites a method for determining the presence of target analytes in a sample by measuring the changes in the electrical properties of an electrode comprising an assay complex comprised of a capture binding ligand attached to the electrode, a target analyte, and an electron transfer moiety. In addition to applying an electronic input signal and detecting an electronic output signal from the electrode, claim 12 recites processing of the output signal to increase the signal-to-noise

ratio; claim 27 recites processing the output signal to determine presence of a target analyte. Thus, subsequent to detecting an output signal (i.e. by cyclic voltammetry or AC voltammetry with a lock-in amplifier), the present claims provide for processing the output signal, for example by joint time frequency transforms and higher harmonic analysis, to refine the signal. The processing allows separating out the background noise and/or increasing signal-to noise-ratio.

Claims 19, 21, and 23 recite processing of the detected output signal by use of a peak recognition scheme, signal averaging, and peak recognition, respectively. When an alternating current source, such as that described by Giancoli, is applied to the electrode of the instant claims, the properties of the electrode (i.e. conductance, impedance, capacitance, redox kinetics etc.) determines the characteristics of the resulting electronic output signal. The present claims recite processing the resulting electronic output signal to characterize and quantitate the electrode response. For example, in one embodiment of peak recognition, a mathematical algorithm, (i.e. Levenberg-Marquardt algorithm) is used to find a best fit between an actual output signal and a theoretical output signal, which models the contributions of the signal and the background noise (see Specification, pages 102-105). Subsequent subtraction of the estimated background allows approximation of the true signal. Thus, "peak recognition" is a procedure applied to analyze the output signal and is disparate from the "peak current" of an AC or DC source.

Applicants respectfully remind the Examiner that the Patent Office bears the initial burden of establishing a prima facie case of obviousness. See In re Bell, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); see also M.P.E.P. § 2142. Although an unexpected result is evidence of nonobviousness, the absence of an unexpected result is not the proper legal standard for a finding of obviousness under § 103(a). Under the patent laws, the following three basic criteria must be met to establish a *prima facie* case of obviousness.

First, the prior art reference must provide one of ordinary skill in the art with the suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention. Thus, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. See WMS Gaming Inc. v. International Game Technology, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references may be found in teachings within the references themselves, the ordinary knowledge of those skilled in the art, or the nature of the problem to be solved. See id. The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. See In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990). see also M.P.E.P. §2 143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would be successful. See In re Dow, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. See M.P.E.P. 706.02(j). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not the Applicant's disclosure. See In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of the above mentioned criteria are not met, *prima facie* obviousness is not established.

Applicants respectfully submit that Megerle in view of Meade fail to teach or suggest each and every element of claims 12, 19, 21 and 23-27. Megerle do not teach or suggest processing an output signal to increase the signal-to-noise ratio as recited in claim 12. Meade describe various methods to detect an output signal (i.e. response) of an electrode upon

application of an input electronic signal, but fail to teach or suggest methods to process the detected output signal.

In contrast, claims 12 and 27 are drawn to processing of the detected output signal to characterize the response of an electrode, especially by separating out the background noise or by increasing the signal-to-noise ratio. These processing techniques include peak recognition schemes, signal averaging, and peak recognition as recited in claims 19, 21 and 23. Processing methods such as peak recognition are unrelated to the definition of "peak currents" of an AC source described in Giancoli. Peak recognition involves, in one aspect, applying mathematical algorithms to analyze the character of an electrode's response while "peak current" is simply a definition of the maximum current generated by an AC source.

Accordingly, Applicants submit that Megerle in view of Meade do not teach or suggest each and every element of claim 12 or 27, and thus fail to render claim 12 or 27 obvious. As claims 24-26 depend from claim 12, they are patentable for at least the same reasons. Moreover, processing of a detected output signal are not inherent properties of an AC or DC source. Thus, Megerele in view of Giancoli do not teach or suggest each and every element of claim 19, 21, or 23, and thus fail to render claim 19, 21, or 23 obvious. In view of the foregoing, Applicants request withdrawal of the rejection under 35 U.S.C. § 103(a).

Claims 12, 16, 21 and 22 are rejected under § 103(a) as being obvious over Megerle in view of Singhal et al. (Anal. Chem (1997) 69: 3552-57) (hereinafter "Singhal"). Applicants respectfully traverse.

Teachings of Megerle have been summarized above.

Singhal teach the detection of purine and pyrimidine-based nucleotides that are free in solution, unattached to an electrode. Singhal describes the method as especially suited to flow-through detection as applied to techniques such as liquid chromatography and capillary electrophoresis (page 3553) where continuous monitoring of sample is required. Singhal expressly dissuades the use of detection schemes using nucleic acids bound to electrodes for

continuous analysis since nucleotides bound to an electrode "foul" the electrodes and limit its usefulness in flow-through methods (page 3552, left column, lines 12-23; page 3553, right column, lines 12-18). Singhal analyzes the electrode response by examining the output signal at harmonic frequencies above the fundamental frequency. Fast Fourier Transform (FFT) algorithms are employed to separate out the frequency domains of the output signal into its constituent harmonic frequencies of the excitation waveform.

The criterias required to establish a *prima facie* case of obviousness under § 103(a) have been set forth above. As a preliminary matter, Applicants note that a reference which teaches away from the claimed invention cannot render the invention obvious. See Dow Chemical Co. v. American Cyanamid Co., 2 USPQ2d 1350 (Fed. Cir. 1987).

Applicants respectfully submit that Megerle in view of Singhal fail to render claims 12, 16, 21 and 22 obvious. Megerle teach use of electrodes having a covalently bound binding ligand, such as a nucleic acid, but fails to teach or suggest processing of an output signal. Singhal teach processing of an output signal by methods such as sinusoidal voltammetry and higher harmonics analysis, but fail to teach or suggest use of such methods as applied to nucleic acids covalently bound to an electrode. Pointedly, Singhal teach away from the limitations of claim 12 by citing the disadvantages of nucleic acids absorbed on surfaces of electrodes for flow through detection schemes. The Examiner has not pointed to where in Singhal the suggestion exists for applying higher harmonic analysis and FFT algorithms, signal averaging, or spectral analysis to output signals detected from electrodes comprising covalently attached nucleic acids. When considered as a whole, Singhal teach away from use of electrodes comprising covalently attached nucleic acids. Thus, Applicants submit that there is no motivation or suggestion in Singhal to combine the teaching of Megerle to arrive at the limitations of claim 12.

Accordingly, Applicants submit that in the absence of a suggestion or motivation to combine the prior art references, Megerle in view of Singhal fail to satisfy the requirements

for establishing a *prima facie* case of obviousness for claim 12. Claims 16, 21, and 22 depend from claim 12 and are thus patentable for the same reasons. In view of the foregoing, Applicants respectfully request the withdrawal of rejections under 35 U.S.C. § 103(a) for claims 12, 16, 21, and 22.

Claims 12 and 17 are rejected under § 103(a) as being obvious over Megerle in view of Cheever et al. (Comput. Appl. Biosci. (1991) 7: 143-45) (hereinafter "Cheever"). Applicants respectfully traverse.

In regards to Cheever, the reference describes use of Fast Fourier Transform (FFT) algorithms for similarity searches of DNA and protein sequences. In Cheever, FFT is used to rapidly compare and align a query sequence, either nucleic acid or protein, to sequences held in a database. The "signal" examined in Cheever is the degree of alignment between the query sequence and database sequences, while the background "noise" is the random matches that occur in an alignment. Cheever uses FFT to detect local similarities that might be otherwise obscured by random matches (i.e. noise) when the query sequence is long.

Applicants submit that Megerle in view of Cheever fail to teach or suggest each and every element of claim 12 and 17. Megerle fail to teach or suggest processing of an electronic output signal to increase the signal-to-noise ratio, as recited in claim 12. Cheever teach applying FFT to "signals" of matching sequences but do not teach or suggest applying FFT to processing of electronic output signals to increase signal-to-noise ratio. Electronic output signals involve complications of electronic background noise, such as capacitance charging currents and bulk impedance (Specification, page 94, lines 27-36), which are disparate from background noise arising from random matches of nucleic acid or protein sequences. Thus, teaching of Cheever is inapplicable to the present claims.

Applicants submit that the Examiner relies on prior art that is not reasonably pertinent to the Applicants' field of endeavor. A prior art reference is reasonably pertinent if the subject matter of the prior art "logically would have commended itself to an inventors's

attention in considering the problem." See Wang Laboratories Inc., v. Toshiba Corp., 26 USPQ2d 1767 (Fed. Cir. 1993); see also M.P.E.P. § 2141.01(a). In the instant case, a person of ordinary skill in electrochemistry dealing with electronic signals and electronic noise would not be reasonably expected or motivated to look to DNA and protein sequence analytical methods.

Accordingly, Applicants submit that both Megerle and Cheever fail to teach or suggest processing of an electronic output signal to increase the signal-to-noise ratio. Thus, Cheever fail to cure the deficiency of Megerle by failing to teach or suggest at least one element of claim 12. Thus, Megerle in view of Cheever fail to satisfy the requirements for establishing a *prima facie* case of obviousness for claim 12. Claim 17 depends from claim 12 and are thus patentable for at least the same reasons. In view of the foregoing, Applicants respectfully request the withdrawal of rejections under 35 U.S.C. § 103(a) for claims 12 and 17.

Claim 18 is rejected under § 103(a) as being obvious over Megerle in view of Cheever and further in view of Wood et al. (IEEE Transactions on Biomedical Engineering, (1992) 39: 730-40) (hereinafter "Wood"). Applicants respectfully traverse.

Teachings of Megerle in view of Cheever have been summarized above.

In regards to Wood, the reference teach analysis of sound frequencies ("cardiac vibrations") emitted by various structures of the heart, such as those arising from contracting ventricles and the opening and closing of heart valves. Wood teach measuring the heart sound frequencies and examination of the its time dependent frequency spectrum by joint time frequency transforms (JTFT).

Applicants submit that Megerle in view of Cheever further in view of Wood fail to teach or suggest each and every element of claim 18. As summarized above, Megerle in view of Cheever do not disclose a method for processing an electronic output signal or processing of an electronic output signal to increase the signal-to-noise ratio. Wood teach applying the

JTFT analysis to sound frequencies but fails to teach or suggest use of joint time frequency transforms to process electronic output signals. As stated above, electronic output signals involve complications of electronic background noise, such as capacitance charging currents and bulk impedance (Specification, page 94, lines 27-36), which are disparate from sound frequencies. Thus, teaching of Wood is inapplicable to the present claims.

As with Cheever, the Examiner relies on prior art in Wood that is not reasonably pertinent to the instant application. A person of ordinary skill in electrochemistry dealing with electronic signals and electronic noise would not be reasonably expected or motivated to look to analysis of sound frequencies.

Accordingly, Applicants submit that Wood fail to cure the deficiency in Megerle and Cheever by failing to provide a necessary element of claims 11-13. Thus, Megerle in view of Cheever, further in view of Wood, either alone or in combination fail to satisfy the requirements for establishing a *prima facie* case of obviousness for claims 11-13. Claim 18 ultimately depends from claims 11-13, and are thus patentable for at least the same reasons. In view of the foregoing, Applicants respectfully request the withdrawal of rejections under 35 U.S.C. § 103(a) for claim 18.

Claims 20 and 22 stand rejected under § 103(a) as being obvious over Megerle in view of Nederlof et al. (Cytometry (1992) 13: 846-52) (hereinafter "Nederlof"). Examiner contends that Nederlof teach processing of electronic output signals by digital filtering or spectral analysis. Applicants respectfully traverse.

In regards to Nederlof, the reference teaches quantifying specific DNA sequences by in situ hybridization. Nederlof use fluorescently labeled nucleic acid probes to determine the number of specific DNA sequences in the nuclei of single cells by acquiring fluorescence signals with a charge coupled device camera (CCD). However, significant local background fluorescence arising from the natural fluorescence of bio-molecules (auto-fluorescence) and non-specific binding of fluorescent probes can mask sequence specific signals. To eliminate

this background fluorescence, Nederlof teach digital filtering, which quantitates the background fluorescence from a set size of the image (i.e. set number of pixels of the CCD camera) and subtracts the background to localize true hybridization signals. Thus, Nederlof teach digital processing of photonic signals (i.e. light signals).

Applicants submit that Megerle in view of Nederlof fail to teach each and every element of claim 20. As summarized above, Megerle fail to teach processing of detected electronic output signals or processing of electronic output signals to increase signal to noise ratio. Nederlof teach processing of photon signals but does not teach processing of detected electronic output signals. Since Nederlof fails to cure the deficiency in Megerle, the references, either alone or in combination fail to teach or suggest each and every element of claim 20. Thus, Megerle in view of Nederlof do not satisfy the requirements for establishing a case of *prima facie* obviousness for claims 11-13. Claim 20 ultimately depends from claims 11-13 and are thus patentable for at least the same reasons. In view of the foregoing, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 103(a) for claim 20.

In regards to teaching of spectral analysis by Nederlof, Applicants were unable to identify a passage in Nederlof cited by the Examiner as reciting processing by spectral analysis. Applicants submit that the Examiner has not clearly explained the basis for rejection of claim 22 based on obviousness as required under 37 C.F.R. § 1.104(c)(2). Accordingly, Applicants request withdrawal of the rejection under § 103 of claim 22.

CONCLUSIONS

Applicants respectfully submit that all pending claims of the above referenced application satisfy all requirements of patentability and are in condition for allowance. Accordingly, early notification of such allowance is earnestly solicited.

Attached hereto is a marked up version of the changes made to the claims by the "Reply To Office Action and Amendment." The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE." In addition, an Appendix of the pending claims is attached for the Examiner's convenience.

If after review, the Examiner feels there are further unresolved issues or determines that prosecution of the instant application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Dated: Dec 20, 2001

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

11. (Amended) A method of [detecting] determining the presence of target analytes in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying an electronic first input signal to said assay complex;

c) [receiving] detecting an electronic output signal;

d) processing said detected output signal to [detect] determine the presence of said target analytes.

12. (Amended) A method of [detecting] determining the presence of target analytes in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying an electronic first input signal to said assay complex;

c) [receiving] detecting an electronic output signal;

d) processing said detected output signal to increase the signal-to-noise ratio and [detect] determine the presence of said target analyte.

13. (Amended) A method of [detecting] determining the presence of target nucleic acid sequences in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture probe covalently attached to said electrode;

ii) a target sequence; and

iii) an electron transfer moiety;

b) applying an electronic first input signal to said assay complex;

c) [receiving] detecting an electronic output signal;

d) processing said detected output signal to [detect] determine the presence of said target sequences.

14. (Amended) A method according to claim [1] 11 or [2] 12 wherein said target analyte is a nucleic acid.

15. (Amended) A method according to claim [1] 11 or [2] 12 wherein said target analyte is a protein.

25. (Amended) A method according to claim 11, 12 or 13 wherein said input signal comprises an alternating current (AC) [AC] component and a direct current (DC) [DC] component.

27. (Amended) A method of [detecting] determining the presence of target analytes in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying a first input signal to said assay complex, wherein said input signal comprises the sum of multiple frequencies at a plurality of amplitudes;

c) [receiving] <u>detecting</u> an output signal;

d) processing said output signal to [detect] <u>determine</u> the presence of said target analytes.

<u>APPENDIX OF PENDING CLAIMS</u>

11. A method of [detecting] <u>determining the presence of</u> target analytes in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying an electronic first input signal to said assay complex;

c) [receiving] <u>detecting</u> an electronic output signal;

d) processing said <u>detected</u> output signal to [detect] <u>determine</u> the presence of said target analytes.

12. A method of [detecting] <u>determining the presence of</u> target analytes in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying an electronic first input signal to said assay complex;

c) [receiving] <u>detecting</u> an electronic output signal;

d) processing said <u>detected</u> output signal to increase the signal-to-noise ratio and [detect] <u>determine</u> the presence of said target analyte.

13. A method of [detecting] <u>determining the presence of</u> target nucleic acid sequences in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture probe covalently attached to said electrode;

ii) a target sequence; and

iii) an electron transfer moiety;

b) applying an electronic first input signal to said assay complex;

c) [receiving] <u>detecting</u> an electronic output signal;

d) processing said <u>detected</u> output signal to [detect] <u>determine</u> the presence of said target sequences.

14. A method according to claim [1] <u>11</u> or [2] <u>12</u> wherein said target analyte is a nucleic acid.

15. A method according to claim [1] <u>11</u> or [2] <u>12</u> wherein said target analyte is a protein.

16. A method according to claim 11, 12 or 13 wherein said processing comprises analysis of higher harmonic signals.

17. A method according to claim 11, 12 or 13 wherein said processing comprises a fast Fourier transform (FFT) analysis.

18. A method according to claim 11, 12 or 13 wherein said processing comprises joint-time frequency transformation (JTFT) analysis.

19. A method according to claim 11, 12 or 13 wherein said processing comprises the use of a peak recognition scheme.

20. A method according to claim 11, 12 or 13 wherein said processing comprises a digital filter.

21. A method according to claim 11, 12 or 13 wherein said processing comprises signal averaging.

22. A method according to claim 11, 12 or 13 wherein said processing comprises spectral analysis.

23. A method according to claim 11, 12 or 13 wherein said processing comprises peak recognition.

24. A method according to claim 11, 12 or 13 wherein said input signal comprises an alternating current (AC) component.

25. A method according to claim 11, 12 or 13 wherein said input signal comprises an <u>alternating current (AC)</u> [AC] component and a <u>direct current (DC)</u> [DC] component.

26. A method according to claim 11, 12 or 13 further comprising applying a plurality of input signals.

27. A method of [detecting] determining the presence of target analytes in a sample comprising:

a) providing an array comprising a plurality of electrodes, at least one of which comprises an assay complex comprising:

i) a capture binding ligand covalently attached to said electrode;

ii) a target analyte; and

iii) an electron transfer moiety;

b) applying a first input signal to said assay complex, wherein said input signal comprises the sum of multiple frequencies at a plurality of amplitudes;

c) [receiving] detecting an output signal;

d) processing said output signal to [detect] determine the presence of said target analytes.